Docket No.: 3493-0170PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Elie LEVERD et al.

Application No.: 10/584,445

Confirmation No.: 4148

Filed: June 22, 2006

Art Unit: 1614

For: PHARMACEUTICAL COPOSITION OF VINFLUNINE WHICH IS INTENDED FOR PARENTERAL ADMINISTRATION PREPARATION METHOD THEREOF AND USE OF SAME

Examiner: T. P. Thomas

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

I, Elie Leverd, do declare and say as follows:

1. I am one of the Inventors of the above-identified application. A copy of my Curriculum Vitae (five pages) is attached showing my qualifications and experience in the area of pharmaceutical formulations.

2. I have reviewed the most recent Office Action dated January 26, 2009 which issued by the US Patent and Trademark Office in connection with the above-identified application. I note that this Office Action includes rejections against the present patent claims based on the combination of two or more of the disclosures of: [1] GlaxoSmithKline ("Prescribing Information; Navelbine (vinorelbine tartrate) Injection", 2002, Nov., pp. 1-17); [2] Duflos '377 (US 6,127,377); [3] Wolgemuth '643 (CA 2,001,643) and [4] Howell ("Anti-vascular effects of

vinflunine...," *British Journal of Cancer* (2001) 84 (2), pp. 290-295.). I offer the following expert opinion relevant to the distinctions between the presently claimed and disclosed invention of the above-identified application and these references cited against the present application.

Evidence of Unexpected, Advantageous Properties of Present Invention

3. The disclosed and presently claimed invention is directed to a vinflunine pharmaceutical composition in the form of a stable and sterile aqueous solution of a water-soluble vinflunine salt at a pH between 3 and 4, which does not contain any sugar, sugar-based polyol or other preservatives, as recited in claim 1. As explained at pages 1-4 of the present specification, conventional pharmaceutical formulations containing vinflunine did not exhibit acceptable storage stability properties or required somewhat complex methods for preparing injectable formulations.

4. The improved stability properties exhibited by the composition of the present invention are evidenced by the test results described in connection with Examples 1 and 2 at pages 8-13 of the present specification. These test results establish that the composition of the present invention exhibits significant, unexpected and advantageously improved storage stability properties without requiring complicated techniques or the presence of one or more preservatives. In this regard, note that Example 1 at pages 8-9 of the present application establishes that vinflunine ditartrate is unexpectedly and advantageously more stable in the form of an aqueous solution according to the present invention, as compared to the "pulverulent" form. Example 2 establishes that the aqueous solution according to the present invention ("unbuffered") exhibited unexpected, advantageously improved stability over several formulations containing different buffers at different pH levels. All of the above-noted references cited in the above Office Action fail to disclose or reasonably suggest that these improved stability properties can be obtained by the aqueous formulation of the present invention.

5. The above-noted advantageous properties exhibited by the aqueous formulation according to the present invention were not conventionally recognized. This is evidenced by the presence of pH buffers and sugar derivatives such as mannitol which are present in the commercialized formulations for vincristine sulfate and vindesine sulfate injection formulations as evidenced by enclosed Exhibit A (Product label from http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=vincristine) and Exhibit B (Eldisine®Injection from RxMed: Pharmaceutical information-Eldisine www.rxmed-com/b.main/b2.pharmaceutical/b2.1.monographs/...), respectively.

Significant Distinctions Between Vinflunine and Vinorelbine

6. As disclosed in Duflos '377, vinflunine is structurally related to vinorelbine, but differs in structure since it includes two fluoro substituents and a saturated bond in one of the heterocyclic rings, such that vinflunine is alternatively named as: 20',20'-difluoro-3',4'-dihydrovinorelbine. Even though vinflunine and vinorelbine may have similar therapeutic properties, these compounds exhibit significantly different physico-chemical properties in at least three areas when in the form of a powder or in the form of an aqueous solution.

7. First, there are significant differences in water solubility: vinorelbine tartrate has a solubility higher than 1000 mg/ml whereas vinflunine tartrate has a solubility equal to only 290 mg/ml.

8. Second, there are significantly different properties exhibited by each in the form of a powder after 6 months of storage at 5°C and 25°C: vinorelbine tartrate degrades such that the major impurity is due to the oxidation of the alcohol group in the vindoline structure, whereas in contrast, vinflunine ditartrate degrades such that the major impurity is 23-0 dimethylvinflunine which is due to the hydrolysis of the ester group of the vindoline structure. Therefore, vinorelbine tartrate and vinflunine ditartrate generate very different major impurities. This is evidenced by enclosed Exhibits C-1 and C-2 which show that vinorelbine tartrate generates the

impurity "S/D6" at 5°C and 25°C over time. Exhibit C-1 describes the impurity "S/D6" and corresponds to a portion of the documents submitted by the Assignee to appropriate regulatory authorities in order to obtain marketing authorization for the product described in the above-identified application. Exhibit C-2 includes two graphs showing the S/D6 content changes at "ambient" temperature (i.e. 25°C) and at "fridge" temperature (i.e. 5 °C). Labels "521", "522" and "524 correspond to different batches which were tested.

9. Third, the process for manufacturing vinflunine is totally different from the process for manufacturing vinorelbine. It is a more complex process since it requires a super acid medium. The differences between these two synthetic routes are illustrated in the enclosed Exhibit D.

10. Fourth, vinorelbine exhibits fungicidal activity after up to 28 days of contact with mold spores, with a slight fungicidal activity after 24 hours of contact. In contrast, vinflunine exhibits no fungicidal activity.

11. Consequently, several significant properties differ between these two compounds, such that one skilled in the art would not conclude it would be predictable to employ one compound in place of another and expect the same physico-chemical properties to be exhibited together with any improved storage stability properties.

12. Vinflunine generally appears to be less stable than vinorelbine since it has a lower solubility. Vinflunine degrades to form a major impurity significantly different from vinorelbine and does not exhibit fungicidal activity as does vinorelbine. Therefore, the behavior and stability of vinflunine in an aqueous solution can not be predicted based on the different physico-chemical properties exhibited by vinorelbine.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

June 26, 2009
Date

Elie Leverd

Enclosures: Curriculum Vitae
Exhibits A, B, C-1, C-2 and D

ADM/lmao

CURRICULUM VITAE

Last name: **LEVERD**
First name: **Elie**
Address: 20, Chemin de Cazers-Bas LAMBERT 81100 CASTRES (France)
Date of birth: 6 december 1948
Place of birth: VERSAILLES (France)
Family status: Married - 2 children

QUALIFICATIONS

Appointed Expert Analyst by decree of 21.02.85 published in the Official Bulletin of the Ministry of Social Affairs and National Solidarity N° 85/12 dated 17.04.85

Chemical Engineer – Diploma from the Higher National School of Chemistry – Montpellier 1971

Baccalaureat in elementary mathematics - 1966

CURRENT FONCTION

Head of Liquid Semi-solid and Parenteral Dosage Forms at the PIERRE FABRE DEVELOPMENT CENTER since 1991

PROFESSIONAL EXPERIENCE

Controller of the Department of Formulation Research and Development for Liquid and Semi-solid Dosage Forms at the PIERRE FABRE RESEARCH CENTER from 1979 to 1991

Responsible for Research in the Formulational Department at the PIERRE FABRE RESEARCH CENTER from 1977 to 1979

Responsible for Research in the Phytochemistry Department at the PIERRE FABRE RESEARCH CENTER from 1973 to 1977

Deputy to the controller for physico-chemical control in the Production Unit at PIERRE FABRE MEDICAMENT (1972)

PATENTS

- NEW ANTACID AGENT AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT
  J.C. TROMBE, G. BONEL, G. MONTEL, F. FAURAN, E. LEVERD, F. MAYNE
  French Patent n° 81.14080

- ANTACID AND ANTI-REFLUX PHARMACEUTICAL COMPOSITION
  J.C. TROMBE, G. BONEL, G. MONTEL, F. FAURAN, E. LEVERD, F. MAYNE
  French Patent n° 81.14081

- INHALER RELEASING PRE-DOSED QUANTITIES OF VOLATILE ACTIVE INGREDIENT OR OBTAINABLE BY A VOLATILE EXCIPIENT CONTAINED IN MICROCAPSULES DISTRIBUTED PERIODICALLY ON A SUPPORT AS WELL AS THE SAID SUPPORT AND ITS MANUFACTURING PROCESS
  M. TRAISNEL, A. GAYOT, P. LETERME, F. MAYNE, E. LEVERD
  French Patent n° 81.21383

- TOOTHPASTE COMPOSITION
  E. LEVERD, M. BAUER, F. MAYNE
  French Patent n° 82.17267

- PHARMACEUTICAL COMPOSITIONS WITH A KERATOLYTIC ACTIVITY IN THE FORM OF HYDRO-ALCOHOLIC GEL
  E. LEVERD, M. LACROUX
  French Patent n° 85.11796

- STABLE AQUEOUS SOLUTION OF VINCRISTINE SULPHATE
  E. LEVERD, M. BAUER, S. BASQUIN
  French Patent n° 86.06030

- PHARMACEUTICAL COMPOSITION FOR THE PARENTERAL ADMINISTRATION OF NAVELBINE
  E. LEVERD, M. BAUER, S. BASQUIN
  French Patent n° 87.15686

- COMPOSITION AND METHOD OF PREPARATION OF A DESONIDE EMULSION
  E. LEVERD, M. LACROUX, D. MROZ-COMBESSIS, J. BOUGARET
  French Patent n° 94.07445

- CUTANEOUS FOAMING PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF *PITYROSPORUM OVALE* INDUCTED DERMATOSIS
  E. LEVERD, M. LACROUX, D. MROZ-COMBESSIS, J. BOUGARET, Ch. MROZ
  French Patent n° 95.13202

- THIXOTROPIC FORMULATIONS FOR FILLING CAPSULES
  E. LEVERD, E. GOUTAY, J. BOUGARET, P. LOMBARDIN, J.L. GROSSIORD, M. SEILLER.
  French Patent n° 9808664
  WO 00/01371

- ANILIDE AND CYCLODEXTRIN COMPLEXES, THEIR PREPARATION AND THEIR USE AS MEDICINE IN PARTICULAR FOR TREATING DYSLIPIDEMIAE
  J. BOUGARET, E. LEVERD, M.D. IBARRA, A.GIL
  French Patent n° 01.04855
  WO 02/083632

- « VINFLUNINE INJECTABLE »
  E. LEVERD, J. BOUGARET, M.D. IBARRA
  French Patent n° 03.15312
  European Patent ....

- STABLE SOLID DISPERSION OF A DERIVATIVE OF VINCA ALKALOID AND PROCESS FOR MANUFACTURING IT
  E. LEVERD, J. BOUGARET, M.D. IBARRA
  French Patent n° 04.14069
  USA 25348
  WO 2006/069938

- FREEZE-DRIED INJECTABLE PHARMACEUTICAL COMBINATION OF SEMISYNTHETIC VINCA ALKALOIDS AND CARBOHYDRATE STABLE AT ROOM TEMPERATURE
  E. LEVERD, J. BOUGARET, M.D. IBARRA
  French Patent N°06.56044
  USA 60/897,059
  WO 2008/080968

- PHARMACEUTICAL COMPOSITION CONTAINING TRIPTOLIDE
  E. LEVERD, J.F. BOE
  EP07008915.6

- TRANSDERMAL PHARMACEUTICAL COMPOSITIONS CONTAINING A STEROIDAL HORMONE
  E. LEVERD, J. BOUGARET
  French Patent n°0759864

- ORAL PHARMACEUTICAL COMPOSITION FOR SOFT CAPSULES CONTAINING VINORELBINE AND METHOD OF TREATMENT
  (Applicant: R.P. SCHERER TECHNOLOGIES, INC.)
  E. LEVERD, J. BOUGARET, M.M. BOHN, N. HEINTZ
  French Patent n°0206886
  USA 10/161,454
  CA 2,388,431
  WO 03/101383

PUBLICATIONS

- DOSAGE DE LA RAUBASINE PAR CHROMATOGRAPHIE EN PHASE LIQUIDE HAUTE PERFORMANCE
  E. LEVERD, D. BEZIAT, P. HATINGUAIS
  Bull. Chim. Farm. 117:27-32, 1978

- DOSAGE DE L'AJMALICINE DANS CATHARANTHUS ROSEUS G. DON
  J. GLEYE, E. LAVERGNE de CERVAL, E. STANISLAS, E. LEVERD, D. BEZIAT, P. HATINGUAIS
  Annales Pharmaceutiques Françaises. 37 : 217-224, 1979

- SAPONOSIDES DE RUSCUS ACULEATUS L. - ETUDE DE LA LIAISON GENINE-GLUCIDE
  P. HATINGUAIS, E. LEVERD
  Travaux de la Société de Pharmacie de MONTPELLIER. 39 :179-186, 1979

- QUALITE DES MATIERES PREMIERES ET MISE EN OEUVRE GALENIQUE
  E. LEVERD
  S.T.P. PHARMA. 4(4) : 327-329, 1988

- ERYFLUID(R) SOLUTION : UNE GALENIQUE ADAPTEE AU TRAITEMENT DE L'ACNE PAPULOPUSTULEUSE A PREDOMINANCE INFLAMMATOIRE
  A. CHIRON, E. LEVERD
  Abstract Dermato. 124 : 60-61, 1991

- PROTOCOLE DE CONTROLE DU PROPULSEUR 134A, PREMIER SUBSTITUT DES CFC
  RAPPORT D'UN GROUPE DE TRAVAIL DU COMITE FRANÇAIS DES AEROSOLS
  S.T.P. PHARMA PRATIQUES 6(2) :106-110, 1996

- GUIDE POUR LA FILTRATION STERILISANTE
  RAPPORT D'UNE COMMISSION SFSTP
  S.T.P. PHARMA PRATIQUES 8(1) : 5-17, 1998

- DEVELOPMENT OF AN EXPERIMENTAL METHOD FOR MEASURING THE ADHESION OF GELIFIED FORMULATIONS USING TEXTURE ANALYSERS
  V. LOVERA, J. BOUGARET, E. LEVERD, E. GOUTAY, P. MICHAUD, F. RODRIGUEZ and C. ROQUES
  S.T.P. PHARMA SCIENCES 8(3) : 183-187, 1998

- StUDY OF THIXOTROPIC BASES FOR THE FILLING OF HARD CAPSULES
  P. LOMBARDIN, M. SEILLER, E. LEVERD, E. GOUTAY, J. BOUGARET and J.L. GROSSIORD
  S.T.P. PHARMA SCIENCES 10(6) : 429-437, 2000

- THIXOTROPIC BASES FOR THE FILLING OF HARD CAPSULES: IN VITRO RELEASE
  P. LOMBARDIN, E. LEVERD, E. GOUTAY, J. BOUGARET, J.L. GROSSIORD and M. SEILLER
  S.T.P. PHARMA SCIENCES 12(2) : 139-142, 2002

- EVOLUTION OF THE INTERACTION OF A NEW CHEMICAL ENTITY, EFLUCIMIBE, WITH γ-CYCLODEXTRIN DURING KNEADING PROCESS
  A. GIL, A. CHAMAYOU, E. LEVERD, J. BOUGARET, M. BARON and G. COUARRAZE
  EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES 23 : 123-129, 2004

Exhibit A

U.S. Food and Drug Administration • Center for Drug Evaluation and Research
FDA Oncology Tools Product Label Details in Conventional Order for vincristine

Select Prescribe for how someone prescribing a medication such as a physician may view the product label section order. Select Prepare for how someone preparing a medication such as a pharmacist or nurse may view the sections Select Administer for how someone administering a medication such as a nurse or patient may view the sections. Please send any errors, omissions, and comments to Send Comment.

Prescribe Prepare Administer

Application	
Supplement Number	014103
Box Warning	
Boxed Warning	Caution- This preparation should be administered by individuals experienced in the administration of vincristine sulfate injection. It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine is injected. Leakage into surrounding tissues during intravenous administration of vincristine sulfate injection may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY. See WARNINGS section for the treatment of patients given intrathecal vincristine sulfate injection.
Complete Label	
Formatted in PDF	ONCOVIN
Description	
Mechanism of Action	Vincristine Sulfate Injection is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant (Vinca rosea Linn). Originally known as leurocristine it has also been referred to as LCR and VCR. The molecular formula for vincristine sulfate is C46H56N4O10 • H2SO4. It has a molecular weight of 923.04. Vincristine sulfate is a white to off-white powder. It is soluble in methanol, freely soluble in water, but only slightly soluble in 95% ethanol. In 98% ethanol, vincristine sulfate has an ultraviolet spectrum with maxima at 221 nm (L+47,100). Vincristine Sulfate Injection, USP is a sterile, preservative-free, single use only solution available for intravenous use in 2 mL (1 mg and 2 mg) vials. Each mL contains vincristine sulfate, 1 mg; mannitol, 100 mg; and water for injection, q.s. Sulfuric acid or sodium hydroxide have been added for pH control. The pH of Vincristine Sulfate Injection ranges from 4.0 to 5.0. At the time of manufacture, the air in the containers is replaced by nitrogen.
Generic Drug Name	vincristine sulfate
Manufacturer	
Manufacturer	Gensia Sicor Pharmaceuticals, Inc. Irvine, CA 92618

Exhibit B

ELDISINE® INJECTION

Lilly

Vindesine Sulfate

Antineoplastic

Action And Clinical Pharmacology: The mode of action of vindesine is not completely understood. Like the other vinca alkaloids, vinblastine sulfate (Velbe) and vincristine sulfate (Oncovin), vindesine causes arrest of cells in metaphase mitosis. In addition, in vitro investigation has demonstrated that vindesine prevents invasion of normal tissue by malignant cells. Comparative studies with these 3 alkaloids, however, demonstrate differences in their effect at the molecular level. Vindesine has been shown to be 3 times more potent than vincristine and nearly 10 times more potent than vinblastine in effecting mitotic arrest in tissue culture studies designed to arrest from 10% to 15% of the cells in mitosis. At dose levels that arrest 40% to 50% of the cells in mitosis, vindesine and vincristine are approximately equipotent, and both have 3 times the potency of vinblastine. In addition, qualitative differences are noted among the 3 alkaloids. At the lower dose, vinblastine produced a predominance of postmetaphase cells in which the midbody and chromosomes were strikingly apparent. In contrast, cells exposed to vincristine displayed a ball-type metaphase with compact chromosomes within a shrunken spindle.

Unlike vinblastine, vindesine produced very few postmetaphase cells. The spindles in cells exposed to vindesine were swollen with dispersed chromosomes, in distinct contrast to the closely packed chromosomes seen with vincristine.

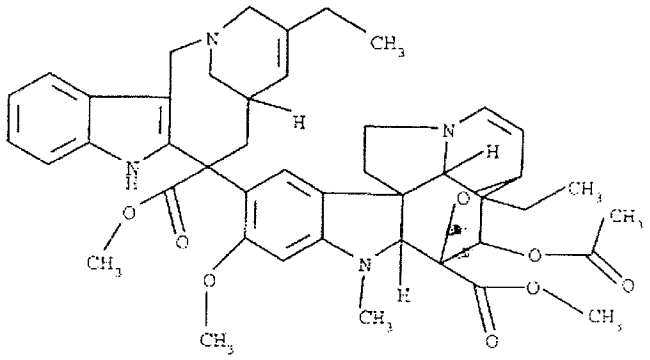
Vindesine has displayed oncolytic activity in patients who have relapsed while on multiple-agent treatment that included vincristine.

In laboratory animals and man, the biliary system is the major route of excretion of vindesine.

Hematologic Effects: Clinically, temporary leukopenia is an expected effect of vindesine and the level of the leukocyte count is an important guide to therapy with this drug. In general, the larger the dose employed, the more profound and longer-lasting the

Extract from CTD – Module 3-Quality – V2 March 2005 :

Impurity A (or S/D6 or 3',4',7,8-tetradehydro,3,4'-dideoxy,3,6-epoxy,6,7-dihydro,-C'-norvincaleukoblastine)

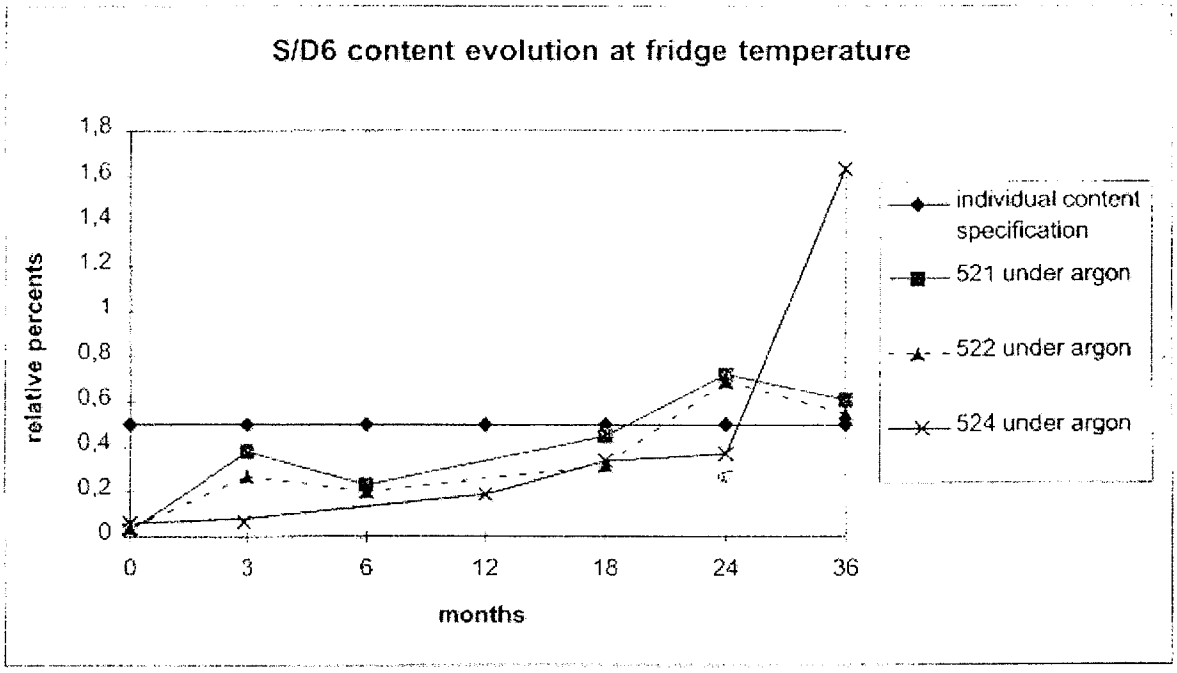


3',4',7,8-tetradehydro,3,4'-dideoxy,3,6-epoxy,6,7-dihydro,-C'-norvincaleukoblastine, labelled impurity A (or S/D6), comes from the oxidation on the vindoline skeleton of vinorelbine.

It's the major degradation product of raw material.

Extract from DCPB – Part II V6 – March 2000:

The evolution of the major impurity S/D6 at ambient and at fridge temperature is plotted in the 2 graphs below for the various batches. The S/D6 content increases after 3 months refrigerated storage and immediately when the powder is exposed to a temperature of around 25°C.



Related substances (by the liquid chromatography system 2001)

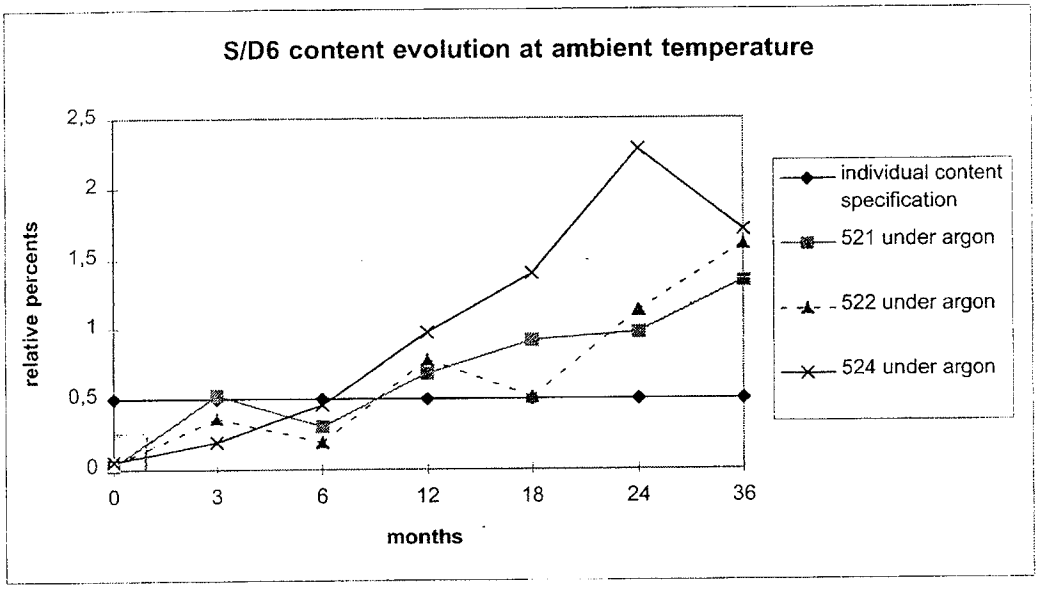
Evolution of major degradation products are summarized below after six months

	BATCH 501		BATCH 503	
	25°C 60% RH	5°C	25°C 60% RH	5°C
23.O.demethylvinflunine	+1.1	+0.2	+0.9	+0.1
6'-N-methylvinflunine	+0.7	+0.2	+0.6	+0.1
Δ-7,8-vinflunine-3,6-ether	no	no	+0.3	no
D11(RRT=0.90)	+0.2	no	+0.2	no
4-O-deacetylvinflunine	+0.1	no	+0.2	no
D5(RRT = 0.24)	+0.1	no	+0.1	no
Total content	+2.3	+0.5	+2.3	+0.3

No= no evolution

Exhibit C-2

The evolution of the major impurity S/D6 at ambient and at fridge temperature is plotted in the 2 graphs below for the various batches. The S/D6 content increases after 3 months refrigerated storage and immediately when the powder is exposed to a temperature of around 25°C.



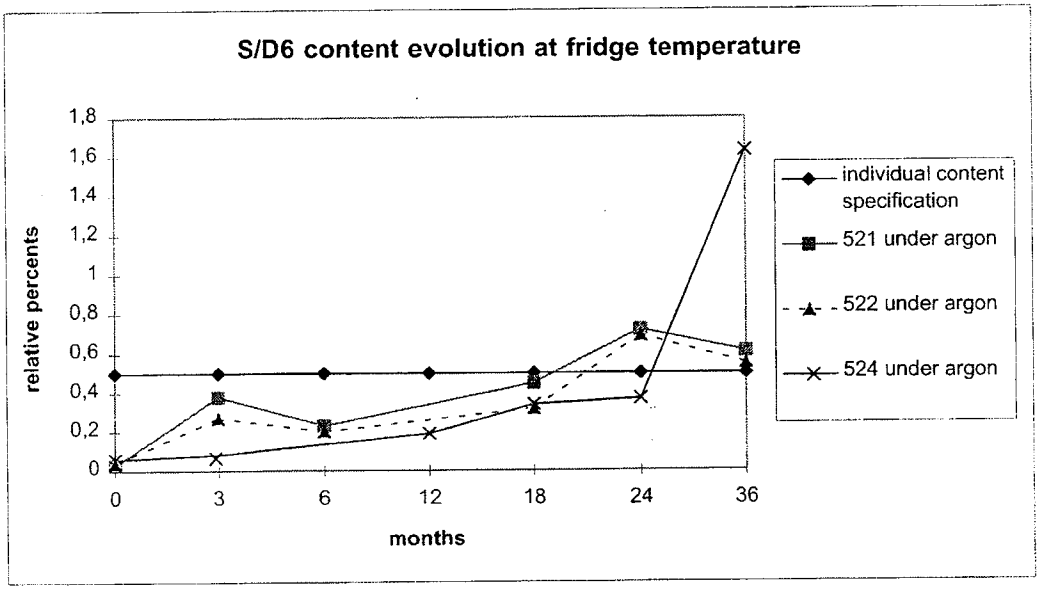
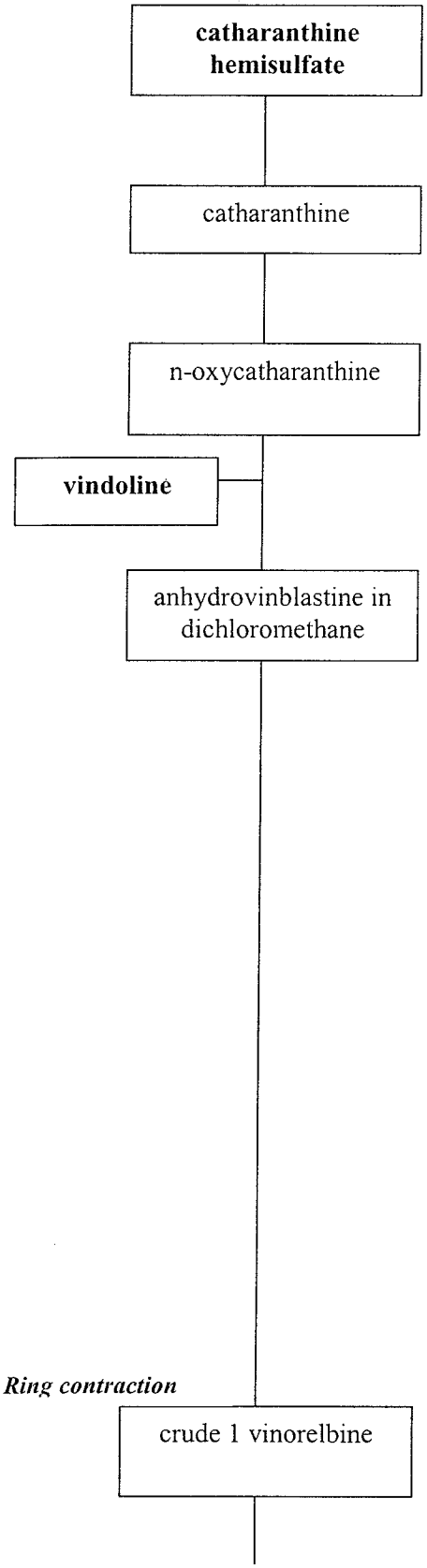
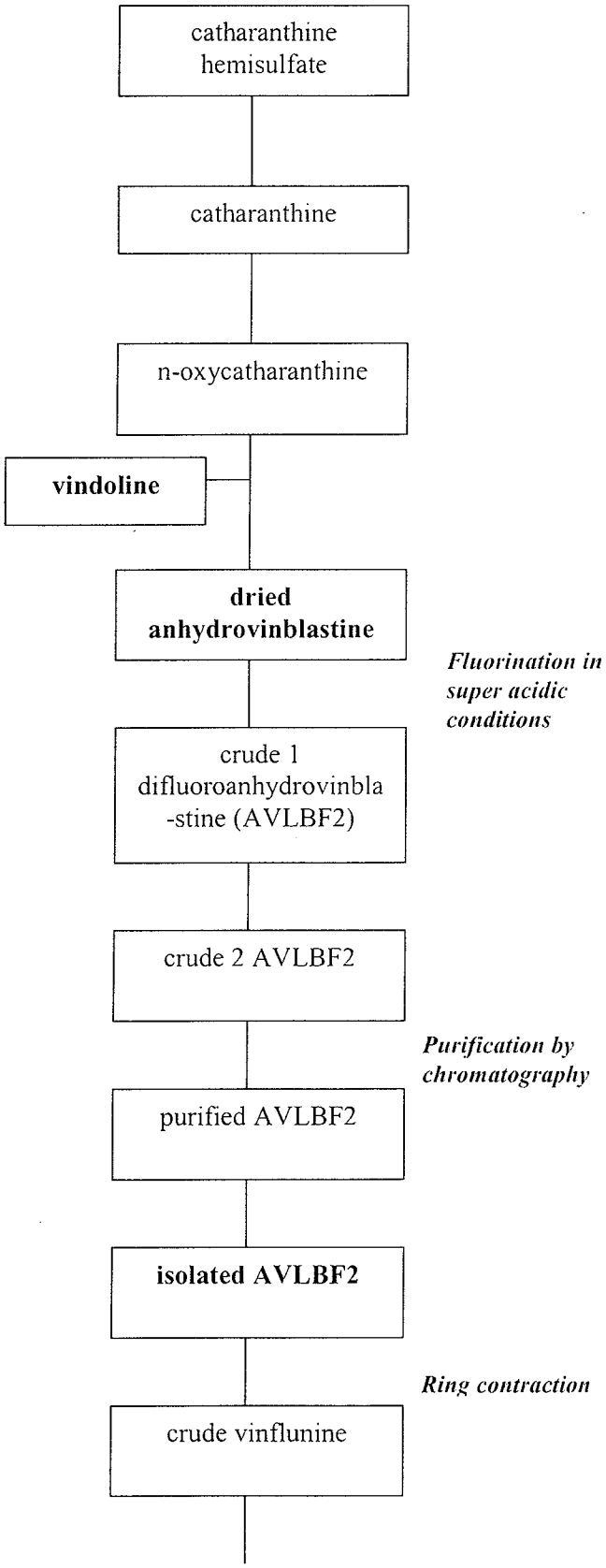


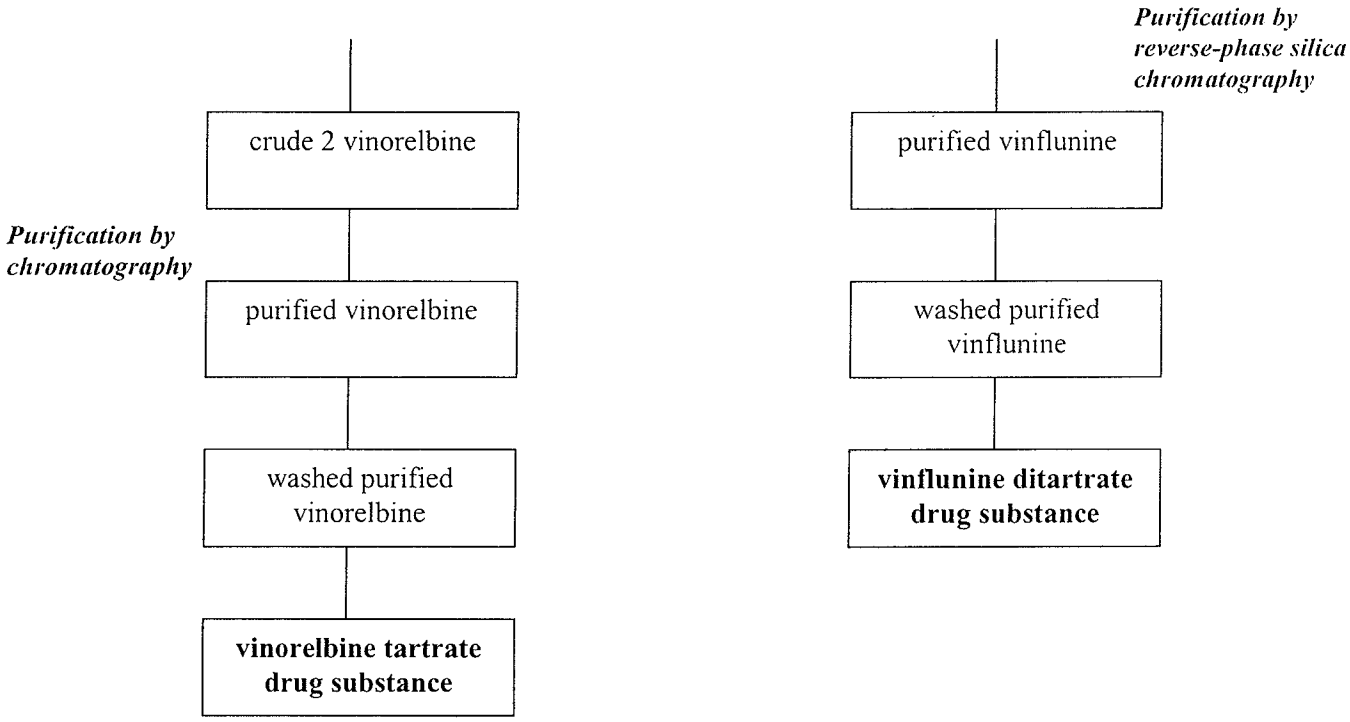
Exhibit D

Synthesis of vinorelbine tartrate



Synthesis of vinflunine ditartrate




crude 2 vinorelbine
Purification by chromatography
purified vinorelbine
washed purified vinorelbine
vinorelbine tartrate drug substance
Purification by reverse-phase silica chromatography
purified vinflunine
washed purified vinflunine
vinflunine ditartrate drug substance